Remarks

The present claims are claims 7-16. Favorable reconsideration of this application is respectfully requested.

Claims 7-16 were rejected under 35 USC 103(a) as unpatentable over Mazuel et al. (US 4,861,760), Rozier (US 5,304,559), and further in view of GB 2007091. Reconsideration is requested.

Mazuel et al. discloses, in Example 3, dexamethasone phosphate solutions (that may or may not turn into gels, and if so, only upon contact with the eye's liquids). At column 2, lines 16 et seq., Mazuel et al. explicitly states that the invention relates to a pharmaceutical composition that "is intended to be administered as a non-gelled liquid form and is intended to gel in situ" meaning that the Mazuel et al. preparation forms a gel only upon contact with the physiological fluid, namely, human lacrimal fluid. Such statements are repeated throughout the cited reference; see, for example, column 2, lines 30-34:

> "the composition, which takes the form of a liquid before its introduction into the eye, undergoes a liquid-gel phase transition, and hence changes from the liquid phase to the gel phase, once it is introduced into the eye, as a result of the ionic strength of the physiological fluid which is in this case, the lacrimal fluid.

In fact, Mazuel et al. teaches away from gel preparations; see, for example, column 2, lines 56 to 61:

> "Furthermore, in the case of already gelled or semi-gelled solid compositions, it is not possible to administer them by volumetric means, especially when they come from a multi-does container."

Previous rejections have referenced the Examples at columns 7-8 of Mazuel et al. However, these examples are also liquid solutions that turn into gels upon contact with the lacrimal fluid. This behavior of the ophthalmic liquid solutions of Mazuel et al. is due to the specific polysaccharide Gelrite®. See, also, column 4, lines 59 et seq., where Mazuel et al. discloses adding acetic acid, if necessary, to avoid gelling of Gelrite solutions; in other words, Mazuel et al. again teaches against gel forms of the solutions, prior to administration to the eye.

Applicant is mindful that the Examiner is entitled to give the claims their broadest reasonable interpretation. However, it is submitted that the present claims do not read on a formulation that gels upon exposure to eye fluid. First, claim 7 clearly states the preparation has the form of a gel. Second, claim 7 stats the preparation has a pH above 7.3 – what would the pH value of the Mazuel et al. formulation be after contacting eye fluid? There is no evidence in Mazuel et al. that such later-formed gels have a pH value above 7.3; in fact, the properties of the later-formed gels are not disclosed at all in this reference.

As Mazuel et al. is only concerned with the aforementioned ophthalmic non-gel solutions, the gel formulations of the present application are clearly not suggested by this reference. In contract, Mazuel et al. teaches away from the gel formulations of the present invention.

Rozier discloses pharmaceutical compositions containing at least one 4-quinolone derivative. Rozier does not cure the deficiencies of Mazuel et al., discussed above.

First, as pointed out above, Mazuel et al. teaches away from gel preparations as claimed. Rozier does not cure this deficiency.

Second, Rozier is concerned with specific ophthalmic preparations containing 4-quinolinone derivatives. Rozier is concerned with preventing crystal growth of these compounds in suspension. There is no mention of storage stable dexamethasone-containing formulations, nor is there any indication that a pH value above 7.3 may be used to increase the stability of a pharmaceutical preparation. In contrast, Rozier teaches that in order to obtain increased stability, an active compound has to be complexed with a certain divalent metal ion.

Third, the rejection alleges that these references also make clear that the use of the claimed pH in ophthalmic field is old. Applicant respectfully submits that such a broad statement does not adequately consider the evidence of record. For example, if dexamethasone dihydrogen phosphate disodium is used as the active compound, one encounters the problem that at pH values around 7.0, stability is reduced so that gel formulations of this compound are not suitable for long term storage conditions as required for pharmaceutical preparations. Why would one skilled in the art select a pH value above 7.3 from the cited references?

GB 2007091 does not cure the deficiencies of Mazuel et al. and Rozier, discussed above. GB 2007091 discloses ophthalmic compositions in the form of a gel, having a pH of 5 to 8. Among Examples 1-40, only Examples 6 and 28 have a pH value above 7.3 (and these examples do not include a dexamethasone).

In the previous Preliminary Amendment, Applicant submitted stability data for an ophthalmic gel preparation of dexamethasone dihydrogenphosphate disodium. Formulation A corresponded to the presently claimed invention. Formulation B is a similar formulation but the pH value was adjusted to 6.3 to 7.3. There was an unacceptable decrease in the amount of dexamethasone dihydrogenphosphate disodium of at least 14% for Formulation B. In contrast, Formulation A of the present invention exhibited only 1% decomposition of dexamethasone dihydrogenphosphate after 18 months.

This previously presented stability data convincingly show that if gel formulations of dexamethasone dihydrogenphosphate disodium are prepared at a pH value above 7.3, the formulations will provide a storage stability required for pharmaceutical preparations.

Accordingly, GB 2007091 does not suggest the presently claimed invention, nor cure the deficiencies of the other cited references. GB 2007091 provides no disclosure regarding the effect of pH on stability of a dexamethasone formulation. Applicant submits that the teachings of GB 2007091 indicate pH is not critical, and therefore, GB 2007091 does not suggest selecting a pH value about 7.3 for a dexamethasone formation. In fact, given that GB 2007091 does not discuss the effect of pH on dexamethasone, this reference is evidence of the nonobviousness of the presently claimed invention.

Stated differently, it was unexpected that by adjusting the pH to the values recited in the claims, ophthalmic gel compositions of dexamethasone dihydrogenphosphate disodium could be obtained that (i) are storage stable and (ii) are not irritating to the human eye. Given that GB 2007091 does not recognize criticality of pH value (and, in fact, leads one skilled in the art to believe that pH is not critical), the claimed formulations are clearly not obvious over the cited references.

The rejection criticized the previously presented data, "since there are so many variables in formulations A and B, which are different from one another". Applicant respectfully disagrees with this assertion. Formulations A and B contain the same

components. The following components are included in both formulations A and B at the same weight percent: Carbopol 980; cetrimide; Na-edetate; and sorbitol. The difference in the weight percentages of the dexamethasone and NaOH are not large, and such differences are what results in different pH values. Stated differently, some variation in the weight percentages of individual components is necessary in order to provide compositions with different pH values. If the two compositions had all the same components at the same weight percentages, the compositions would have the same pH value.

The rejection also criticized the previously presented data as "not commensurate in scope with the claimed language". Applicant does not understand why the data is considered not commensurate in scope with the claims. If the rejection is maintained, clarification is requested (such as a suggested comparative showing that is considered commensurate with the claims, or claimed subject matter than is considered commensurate with the comparative data of record).

A favorable action in the form of a Notice of Allowance is respectfully requested. The Examiner is invited to contact the undersigned to resolve any remaining issues.

Respectfully submitted,

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Dated: November 11, 2005